Addressing the Interface of Anemia, Hemorrhage and Adverse Pregnancy Outcomes

Richard J. Derman, MD, MPH, FACOG
Associate Provost, Global Affairs
Director, Global Health Research
Professor, Obstetrics and Gynecology
Thomas Jefferson University, Philadelphia, Pennsylvania USA

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Preventable Deaths Every Day

- 830 women die during pregnancy and childbirth everyday
- 287,000 maternal deaths every year (total 303,000)
- 56,000 maternal deaths every year in India

WHO, State of World’s Mothers Report 2015
Why Do Women Die?

• Major complications account for 80% of all maternal deaths
• Severe bleeding (primary PPH) – 35%
• ↑ - BP (eclampsia, pre-eclampsia) – > 15 %
• Infections (usually manifest post delivery)
• Confounders include underlying anemia, malaria, HIV/AIDS and TB

WHO, 2012
Anemia in Pregnancy

• Anemia in pregnancy is the major contributor or sole cause of 20-40% of maternal deaths
  -(estimated to affect 41.8% of all pregnant women world)

• Accounts for 8.8% of total disability from all conditions

Bailey, RL et al., the Epidemiology of Global Micronutrient Deficiencies, 2015
Kassebaum, et al., A Systematic Analysis of Global Anemia Burden from 1990 to 2010, 2018
The Lower the Hemoglobin
the Worse the Pregnancy Outcomes for Mother and Baby

• In mothers—
  • ↑ in postpartum hemorrhage
  • ↑ in C/S
  • ↑ in sepsis
  • ↑ preterm births (the leading cause of < 5 mortality)

• In newborns—
  • ↑ low birthweight
  • ↑ stillbirths
  • ↓ cognitive performance
  • ↓ physical growth
  • ↑ behavioral deficits

Lozoff B, Iron deficiency and child development, 2007
Iron Demands in Pregnancy

Are increased 2-3X’s to:

- Address an increase in fluid volume (30%)
- Support the growing fetus (especially in the 2nd half of pregnancy)
- Account for blood loss at delivery

McMahon LP, Iron deficiency in pregnancy, 2010
Ferritin Level

• Measurement of hemoglobin alone is insufficient to determine who will benefit from supplemental iron

• Ferritin is a protein that stores iron and releases it in a controlled fashion

• We now know that maternal levels of serum ferritin of <15 mcg/L predict inadequate iron to the fetal brain

• Once this occurs, the impact to the infant and child is irreversible

Hallberg L et al., Screening for iron deficiency: an analysis based on bone-marrow examinations and serum ferritin determinations in a population sample of women, 1993
Iron Intake

- Despite all national programs supporting supplementation with oral iron, little has changed over the past 40 years
  - Side effects
  - Adherence
  - Poor absorption

Intergenerational Impact

Micronutrient deficiencies have consequences throughout an individual’s life span and are perpetuated across the generations.

Infancy
- Low birth weight
- Higher mortality rate
- Impaired mental development
- Increased risk of chronic disease

Adolescence
- Stunted
- Reduced mental capacity
- Frequent infections
- Fatigue

Childhood
- Stunted
- Reduced mental capacity and productivity
- Frequent infections
- Inadequate growth
- Higher mortality rate

Adulthood
- Reduced productivity
- Poor socioeconomic status
- Malnourished
- Increased perinatal complications and mortality

Childhood
- Stunted
- Reduced mental capacity
- Frequent infections
- Inadequate growth
- Higher mortality rate

British Blood Transfusion Society Recommendation

- Intravenous iron should be considered in women with severe IDA (hemoglobin < 8 gm/dL) or in any newly diagnosed anemia beyond 34 weeks of gestation
- Hemoglobin with < 10 mg/dL may not allow the transfer of sufficient iron to the newborn
- Should be considered in women with confirmed IDA who fail to respond or are intolerant to oral iron

www.bbts.org.uk (amended)
New Approach

• One new therapeutic approach is the expanded use of IV Iron
  • New formulations (4) allow for reduction of anemia (up to 95%) with a single infusion
  • No major serious adverse events in multiple randomized prospective trials from the developed world (> 100 published studies, including its use in pregnancy)
  • Acute need for research to study maternal and infant outcomes in countries where rates of moderate/severe anemia are highest

The RAPIDIRON Trial

Two primary outcomes:

- Rate of conversion to a non-anemic state (>11 g/dL) at the time of delivery.
  (Consistent with GoI strategy to reduce anemia by 3%/year)
- Rate of low birthweight (under 2500 gms)
  (VLBW rates will also be reported)

This reflects a composite outcome, as PTB and IUGR are often associated with low birth weight
The Challenge

• Every 4 minutes a woman dies from postpartum hemorrhage (PPH – 35% of all maternal deaths)

• Global action to address PPH comprehensively is a public health imperative.

USAID/CHIP 2012/ACOG, 2015
Average Interval from Onset to Death

- Ruptured uterus: 24 hours
- Antepartum hemorrhage: 12 hours
- Postpartum hemorrhage: 2 hours (dire implications for women with moderate/severe anemia)

Maine D. Safe Motherhood Programs: Options and Issues, Center for Population & Family Health, Columbia University, 1993
What have we learned about reducing the incidence of PPH from hundreds of published clinical trials?
Active Management of 3rd Stage of Labor

- 5 randomized trials
- Cochrane review
- N = > 6,000
- NNT: Prevent PPH 500 ml - 12
  Severe PPH 1000 ml - 55
Uterotonic Drugs

• Oxytocin-posterior pituitary extract
• Ergometrine-preparation of ergot
• Syntometrine-combination of oxytocin and ergometrine
• Misoprostol-prostaglandin E1 analogue
• Carbetocin (large multi-site clinical trial)
Primary Hypothesis

Misoprostol administered during the third stage of labor will significantly reduce the incidence of acute postpartum hemorrhage by 50%.

N=1600
Measuring postpartum blood loss

• BRASSS-V® blood collection drape with calibrated receptacle

• The drape is used in both arms

Number Needed to Treat (NNT)

One case of postpartum hemorrhage was prevented for every 18 women who received misoprostol.

PPH ↓ 47%
Severe PPH ↓ 80%
India: Misoprostol to Prevent PPH

The Lancet

Oral misoprostol in preventing postpartum haemorrhage in resource-poor communities: a randomised controlled trial


Lancet 2006; 368: 1248-53
Misoprostol for Self-Administration

- Uganda (Mama Miso Study)
- Indonesia (JHPEIGO)
- Afghanistan (JHPEIGO)
- Liberia (JHPEIGO)
- Papua New Guinea
- Tanzania
- Ethiopia
- Nigeria
- Lao People’s Democratic Republic
Misoprostol Registration Completed
Management of PPH Low Resource Settings

Uterine tamponade

- 90% of PPH in under-resourced countries due to uterine atony
- Hydrostatic Balloon Catheters

Tying the condom to the catheter
Non-inflatable Anti-shock Garment
New Drugs to Prevent or Treat PPH

Tranexamic Acid
• Prevents breakdown of fibrin and helps to maintain clotting
• Cochrane review-
  • 12 trials (N=3285) ↓ blood loss after delivery
• WOMAN trial
  • N=20,000 – 20% reduction in blood loss

Carbetocin - heat stable relative of oxytocin
• Positive side effect profile
• Significant reduction in post-c/s blood loss
• Major WHO trial (includes our site) ongoing
Maternal Mortality Due to PPH in the Developing World

- Lack of antepartum screening and treatment for anemia
- Poor access to skilled providers/suppliers
- Poor transport systems
- Poor emergency services
- Poor clinic/hospital infrastructure
- ↑ in unnecessary C/S
- Need for team training, including the use of simulation
The best predictor of a pregnancy outcome... is the state of health of a woman... when she first enters pregnancy
Special Thanks